Clean Version of Replacement Claims

1

569. (Twice Amended) A process for determining the sequence of a nucleic acid of interest, comprising the steps of:

providing or generating detectable non-radioactively labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactively modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said one or more detectable non-radioactively modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety, or the base analog thereof;

subjecting said detectable non-radioactively labeled fragments to a sequencing gel to separate or resolve said fragments; and

detecting non-radioactively the presence of each of said separated or resolved fragments by means of said detectable non-radioactively modified or labeled nucleotides or nucleotide analogs, and determining the sequence of said nucleic acid of interest.

2

586. (Twice Amended) The process according to claim 569, wherein the detectable non-radioactively labeled complementary nucleic acid is fragmented prior to separation in said sequencing gel.

3

587. (Amended) The process according to claim 569, wherein said providing or generating step, the one or more non-radioactively modified or labeled nucleotides or nucleotide analogs have been incorporated into said nucleic acid fragment or fragments.

588. (Amended) The process according to claim 587, wherein at least one of said non-radioactively modified or labeled nucleotides or nucleotide analogs is at a terminus of said fragment or fragments.

X4

600. (Amended) The process according to claim 569, wherein said providing or generating step, the non-radioactively modified or labeled nucleotides or nucleotide analogs comprise one or more members selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

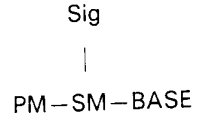
SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety or a base analog of any of the foregoing; and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

(ii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety, and

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii) a nucleotide or nucleotide analog, said nucleotide having the formula

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

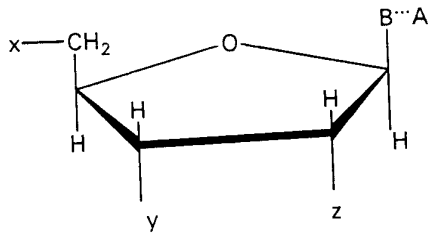
SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group.

601. (Amended) The process according to claim 569, wherein said providing or generating step, the non-radioactively modified or labeled nucleotides or nucleotide analogs have the structure:

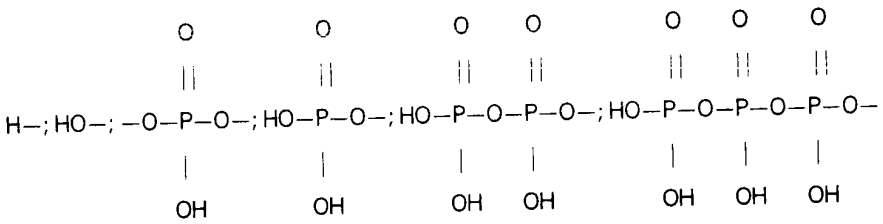


wherein B represents a purine moiety, a 7-deazapurine moiety, a pyrimidine moiety, or an analog of any of the foregoing, and B is covalently bonded to the C1' position of the sugar moiety or sugar analog, provided that whenever B is a purine, a purine analog, a 7-deazapurine moiety or a 7-deazapurine analog, the sugar moiety or sugar analog is attached at the N9 position of the purine moiety, the purine analog, the 7-deazapurine moiety or the 7-deazapurine analog thereof, and whenever B is a pyrimidine moiety or a pyrimidine analog, the sugar moiety or sugar analog is attached at the N1 position of the pyrimidine moiety or the pyrimidine analog;

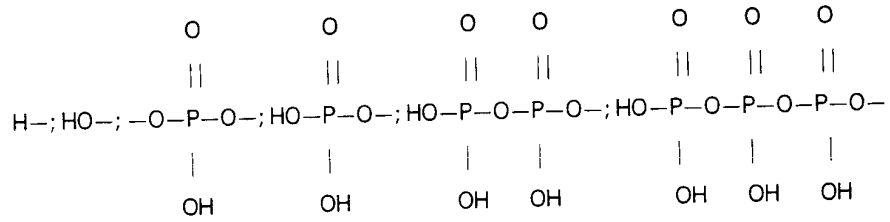
wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety capable of producing directly or indirectly a detectable non-radioactive signal; and

wherein B and A are covalently attached directly or through a linkage group, wherein if B is a purine or a purine analog, A is attached to the 8-position of the purine or purine analog, if B is a 7-deazapurine or 7-deazapurine analog, A is attached to the 7-position of the deazapurine or deazapurine analog, and if B is a pyrimidine or a pyrimidine analog, A is attached to the 5-position of the pyrimidine or pyrimidine analog; and

wherein x comprises a member selected from the group consisting of:



wherein y comprises a member selected from the group consisting of:



wherein z comprises a member selected from the group consisting of H– and HO–.

602. (Amended) The process according to claim 601, wherein y and z are H–.

624. (Amended) The process according to claim 621, wherein said linkage group does not substantially interfere with formation of the signaling moiety or detection of the detectable non-radioactive signal.

X6 713. (Amended) The process according to claim 709, wherein said detecting step is carried out by means of a directly detectable signal provided by said one or more non-radioactively modified or labeled nucleotides or nucleotide analogs, said A or said Sig detectable non-radioactive moiety.

714. (Amended) The process according to claim 713, wherein in said detecting step the directly detectable signal comprises a member selected from the group consisting of a chelating compound, a fluorogenic compound, a chromogenic compound, a chemiluminescent compound and an electron dense compound.

X7 716. (Twice Amended) The process according to claims 569, 600 or 601, wherein said detecting step is carried out by means of an indirectly detectable signal provided by said one or more non-radioactively modified or labeled nucleotides or nucleotide analogs, said A or said Sig detectable non-radioactive moiety.

X8 719. (Twice Amended) The process according to claim 569, wherein said detectable non-radioactively modified or labeled nucleotides or nucleotide analogs are capable of being detected non-radioactively by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

X9 720. (Amended) The process according to claim 569, wherein said detecting step comprises localizing said non-radioactively labeled nucleic acid fragments by means of said detectable non-radioactively modified or labeled nucleotides or nucleotide analogs.

X10

721. (Twice Amended) A process for determining the sequence of a nucleic acid of interest, comprising the steps of:

providing or generating detectable non-radioactively labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactively modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said one or more detectable non-radioactively modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety, or the base analog thereof;

introducing or subjecting said detectable non-radioactively labeled fragments to a sequencing gel;

separating or resolving said fragments in said sequencing gel; and

detecting non-radioactively each of the separated or resolved fragments; and determining the sequence of said nucleic acid of interest.

X11

738. (Twice Amended) The process according to claim 721, wherein the detectable non-radioactively labeled complementary nucleic acid is fragmented prior to separation in said sequencing gel.

X12

739. (Amended) The process according to claim 721, wherein said providing or generating step, the one or more non-radioactively modified or labeled nucleotides or nucleotide analogs have been incorporated into said nucleic acid fragment or fragments.

740. (Amended) The process according to claim 739, wherein at least one of said non-radioactively modified or labeled nucleotides or nucleotide analogs is at a terminus of said fragment or fragments.

X13

752. (Amended) The process according to claim 721, wherein said providing or generating step, the non-radioactively modified or labeled nucleotides or nucleotide analogs comprise one or more members selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

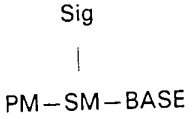
SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety or a base analog of any of the foregoing; and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

(ii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii) a nucleotide or nucleotide analog, said nucleotide having the formula

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

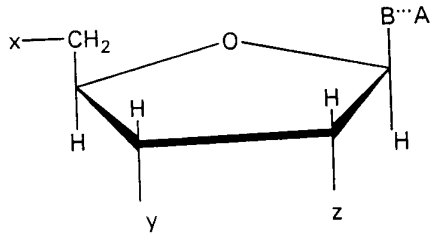
BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group.

753. (Amended) The process according to claim 721, wherein in said providing or generating step, the non-radioactively modified or labeled nucleotides or nucleotide analogs have the structure:

(i)



wherein B represents a purine moiety, a 7-deazapurine moiety, a pyrimidine moiety, or an analog of any of the foregoing, and B is covalently bonded to the C1'-position of the sugar moiety or sugar analog, provided that whenever B is a purine, a purine analog, a 7-deazapurine moiety or a 7-deazapurine analog, the sugar moiety or sugar analog is attached at the N9 position of the purine moiety, the purine analog, the 7-deazapurine moiety or the 7-deazapurine analog thereof, and whenever B is a pyrimidine moiety or a pyrimidine analog, the sugar moiety or sugar analog is attached at the N1 position of the pyrimidine moiety or the pyrimidine analog;

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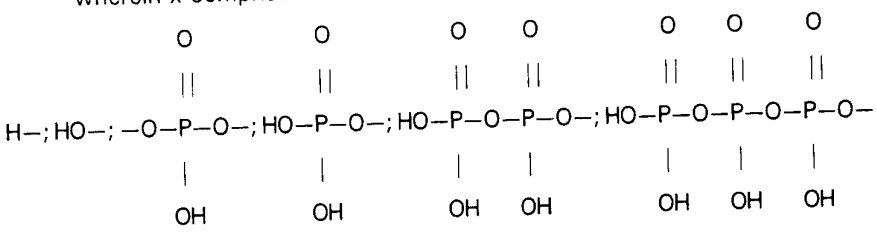
wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety capable of producing directly or indirectly a detectable non-radioactive signal; and

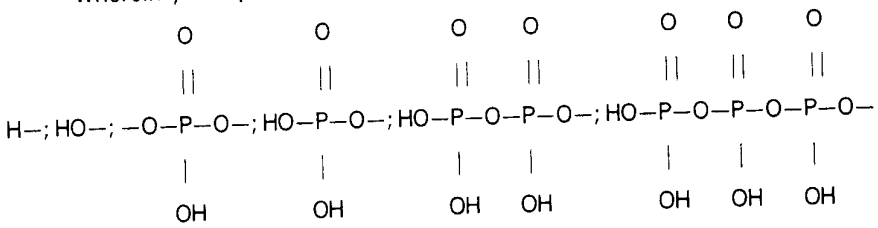
wherein B and A are covalently attached directly or through a linkage group,

wherein if B is a purine or a purine analog, A is attached to the 8-position of the purine or purine analog, if B is a 7-deazapurine or 7-deazapurine analog, A is attached to the 7-position of the deazapurine or deazapurine analog, and if B is a pyrimidine or a pyrimidine analog, A is attached to the 5-position of the pyrimidine or pyrimidine analog; and

wherein x comprises a member selected from the group consisting of:



wherein y comprises a member selected from the group consisting of:



wherein z comprises a member selected from the group consisting of H– and HO– .

13

754. (Amended) The process according to claim 753, wherein y and z are H– .

14

776. (Amended) The process according to claim 773, wherein said linkage group does not substantially interfere with formation of the signaling moiety or detection of the detectable non-radioactive signal.

X15 859. (Twice Amended) The process according to claim 721, wherein said detectable non-radioactively labeled nucleic acid fragments are detectable by a non-radioactive means selected from the group consisting of a fluorescent measurement, a chemiluminescent measurement, and a combination thereof.

X16 866. (Amended) The process according to claim 865, wherein in said detecting step the directly detectable signal comprises a member selected from the group consisting of a chelating compound, a fluorogenic compound, a chromogenic compound, a chemiluminescent compound and an electron dense compound.

X17 868. (Amended) The process according to claims 721, 752 or 753, wherein said detecting step is carried out by means of a indirectly detectable signal provided by said one or more non-radioactively modified or labeled nucleotides or nucleotide analogs, said A or said Sig detectable non-radioactive moiety.

X18 871. (Twice Amended) The process according to claim 721, wherein said one or more modified or labeled nucleotides or nucleotide analogs are capable of being detected by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

X19 872. (Twice Amended) The process according to claim 721, wherein said detecting step comprises localizing said detectable non-radioactive labeled nucleic acid fragments by means of said one or more non-radioactive modified or labeled nucleotides or nucleotide analogs.

873. (Twice Amended) A process for determining the sequence of a nucleic acid of interest, comprising the steps of:

providing or generating detectable non-radioactive labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety or the base analog thereof;

X19 detecting non-radioactively the detectable non-radioactive labeled nucleic acid fragments with a sequencing gel; and

determining the sequence of said nucleic acid of interest.

X20 890. (Twice Amended) The process according to claim 873, wherein the detectable non-radioactive labeled complementary nucleic acid is fragmented and separated prior to detecting in said sequencing gel.

X21 891. (Amended) The process according to claim 873, wherein in said providing or generating step, the one or more non-radioactive modified or labeled nucleotides or nucleotide analogs have been incorporated into said nucleic acid fragment or fragments.

892. (Amended) The process according to claim 891, wherein at least one of said non-radioactive modified or labeled nucleotides or nucleotide analogs is at a terminus of said fragment or fragments.

X22

904. (Amended) The process according to claim 873, wherein in said providing or generating step, the non-radioactive modified or labeled nucleotides or nucleotide analogs comprise one or more members selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

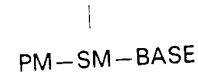
SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety or a base analog of any of the foregoing; and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

(ii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii) a nucleotide or nucleotide analog, said nucleotide having the formula

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

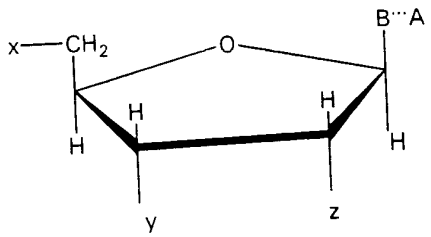
BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group.

905. (Amended) The process according to claim 873, wherein in said providing or generating step, the non-radioactive modified or labeled nucleotides or nucleotide analogs have the structure:

(i)



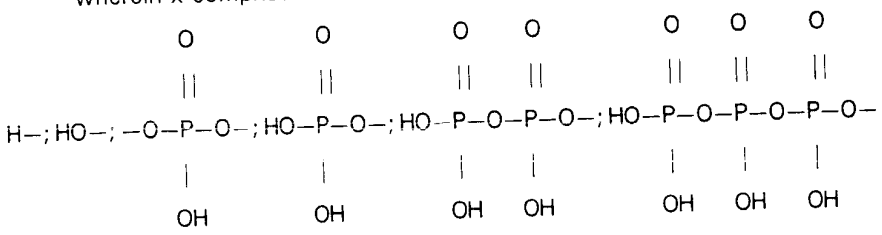
wherein B represents a purine moiety, a 7-deazapurine moiety, a pyrimidine moiety or an analog of any of the foregoing, and B is covalently bonded to the C1'-position of the sugar moiety or sugar analog, provided that whenever B is a purine, a purine analog, a 7-deazapurine moiety or a 7-deazapurine analog, the sugar moiety or sugar analog is attached at the N9 position of the purine moiety, the purine analog, the 7-deazapurine moiety or the 7-deazapurine analog thereof, and whenever B is a pyrimidine moiety or a pyrimidine analog, the sugar moiety or sugar analog is attached at the N1 position of the pyrimidine moiety or the pyrimidine analog;

wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety capable of producing directly or indirectly a detectable non-radioactive signal; and

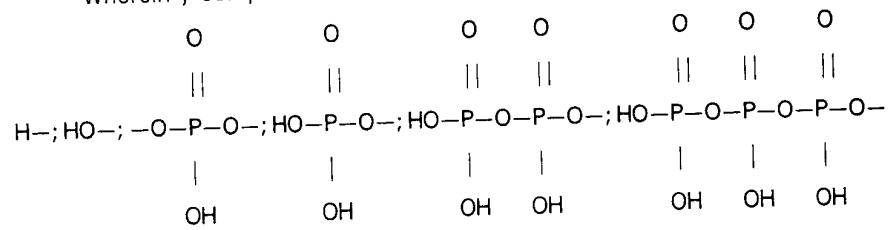
wherein B and A are covalently attached directly or through a linkage group,

wherein if B is a purine or a purine analog, A is attached to the 8-position of the purine or purine analog, if B is a 7-deazapurine or 7-deazapurine analog, A is attached to the 7-position of the deazapurine or deazapurine analog, and if B is a pyrimidine or a pyrimidine analog, A is attached to the 5-position of the pyrimidine or pyrimidine analog; and

wherein x comprises a member selected from the group consisting of:



wherein y comprises a member selected from the group consisting of:



wherein z comprises a member selected from the group consisting of H– and HO–.

906. (Amended) The process according to claim 905, wherein y and z are H– .

928. (Amended) The process according to claim 925, wherein said linkage group does not substantially interfere with formation of the signaling moiety or detection of the detectable non-radioactive signal.

X24 1011. (Twice Amended) The process according to claim 873, wherein said detectable non-radioactive labeled nucleic acid fragments are detectable by a non-radioactive means selected from the group consisting of a fluorescent measurement, a chemiluminescent measurement, and a combination thereof.

1012. (Twice Amended) The process according to claim 873, wherein said detecting step, the detectable non-radioactive labeled nucleic acid fragments are separated or resolved electrophoretically.

X25 1017. (Amended) The process according to claim 1016, wherein said detecting step is carried out by means of a directly detectable signal provided by said one or more non-radioactive modified or labeled nucleotides or nucleotide analogs, said A or said Sig detectable non-radioactive moiety.

1018. (Amended) The process according to claim 1013, wherein said detecting step the directly detectable signal comprises a member selected from the group consisting of a chelating compound, a fluorogenic compound, a chromogenic compound, a chemiluminescent compound and an electron dense compound.

X26 1020. (Amended) The process according to claims 873, 904 or 905, wherein said detecting step is carried out by means of an indirectly detectable signal provided by said one or more non-radioactive modified or labeled nucleotides or nucleotide analogs, said A or said Sig detectable non-radioactive moiety.

X27 1023. (Twice Amended) The process according to claim 873, wherein said one or more non-radioactive modified or labeled nucleotides or nucleotide analogs are capable of being detected by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

X28 1024. (Twice Amended) The process according to claim 873, wherein said detecting step comprises localizing said detectable non-radioactive labeled nucleic acid fragments by means of said one or more non-radioactive modified or labeled nucleotides or nucleotide analogs.

SUB (II)6 1025. (Twice Amended) A process for determining the sequence of a nucleic acid of interest, comprising the step of detecting non-radioactively with a sequencing gel one or more detectable non-radioactive labeled nucleic acid fragments comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs have been modified on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the base moiety or the base analog thereof.

X29 1042. (Twice Amended) The process according to claim 1025, wherein the detectable non-radioactive labeled complementary nucleic acid is fragmented prior to separation in said sequencing gel.

X30 SUB (II)3 1043. (Amended) The process according to claim 1025, wherein said providing or generating step, the one or more non-radioactive modified or labeled nucleotides or nucleotide analogs have been incorporated into said nucleic acid fragment or fragments.

1044. (Amended) The process according to claim 1043, wherein at least one of said non-radioactive modified or labeled nucleotides or nucleotide analogs is at a terminus of said fragment or fragments.

X31

1056. (Amended) The process according to claim 1025, wherein said providing or generating step, the non-radioactive modified or labeled nucleotides or nucleotide analogs comprise one or more members selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

SUB (ff) 30

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

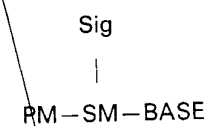
SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety or a base analog of any of the foregoing; and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

(ii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii) a nucleotide or nucleotide analog, said nucleotide having the formula

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

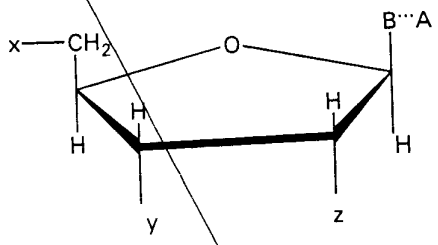
BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group.

1057. (Amended) The process according to claim 1025, wherein said providing or generating step, the non-radioactive modified or labeled nucleotides or nucleotide analogs have the structure:

(i)



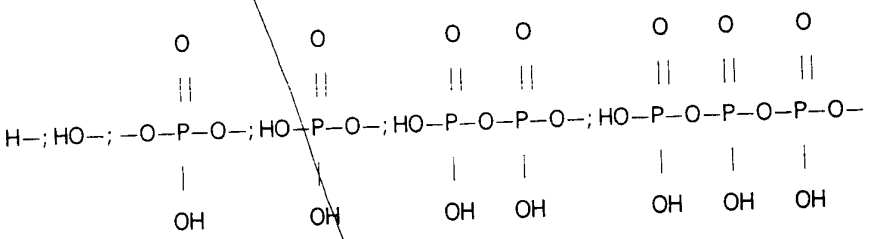
wherein B represents a purine moiety, a 7-deazapurine moiety, a pyrimidine moiety, or an analog of any of the foregoing, and B is covalently bonded to the C1'-position of the sugar moiety or sugar analog, provided that whenever B is a purine, a purine analog, a 7-deazapurine moiety or a 7-deazapurine analog, the sugar moiety or sugar analog is attached at the N9 position of the purine moiety, the purine analog, the 7-deazapurine moiety or the 7-deazapurine analog thereof, and whenever B is a pyrimidine moiety or a pyrimidine analog, the sugar moiety or sugar analog is attached at the N1 position of the pyrimidine moiety or the pyrimidine analog;

wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety capable of producing directly or indirectly a detectable non-radioactive signal; and

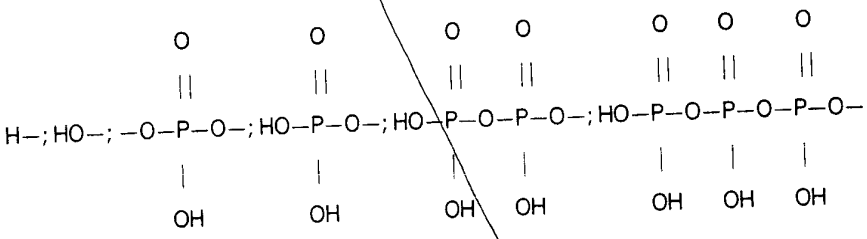
wherein B and A are covalently attached directly or through a linkage group,

wherein if B is a purine or a purine analog, A is attached to the 8-position of the purine or purine analog, if B is a 7-deazapurine or 7-deazapurine analog, A is attached to the 7-position of the deazapurine or deazapurine analog, and if B is a pyrimidine or a pyrimidine analog, A is attached to the 5-position of the pyrimidine or pyrimidine analog; and

wherein x comprises a member selected from the group consisting of:



wherein y comprises a member selected from the group consisting of:



wherein z comprises a member selected from the group consisting of H– and HO–.

1058. (Amended) The process according to claim 1057, wherein y and z are H– .

1164. (Twice Amended) The process according to claim 1025, wherein said detecting step, the detectable non-radioactive labeled nucleic acid fragments are separated or resolved electrophoretically.

X33 1169. (Amended) The process according to claim 1165, wherein said detecting step is carried out by means of a directly detectable signal provided by said one or more non-radioactive modified or labeled nucleotides or nucleotide analogs, said A or said Sig detectable non-radioactive moiety.

1170. (Amended) The process according to claim 1165, wherein said detecting step the directly detectable signal comprises a member selected from the group consisting of a chelating compound, a fluorogenic compound, a chromogenic compound, a chemiluminescent compound and an electron dense compound.

X34 1172. (Amended) The process according to claims 1025, 1056 or 1057, wherein said detecting step is carried out by means of an indirectly detectable signal provided by said one or more non-radioactive modified or labeled nucleotides or nucleotide analogs, said A or said Sig detectable non-radioactive moiety.

X35 1175. (Twice Amended) The process according to claim 1025, wherein said one or more modified or labeled nucleotides or nucleotide analogs are capable of being detected by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

X36 1176. (Twice Amended) The process according to claim 1025, wherein said detecting step comprises localizing said detectable non-radioactive labeled nucleic acid fragments by means of said one or more modified or labeled nucleotides or nucleotide analogs.

1177. (Twice Amended) A process for determining with a sequencing gel the presence of nucleic acid fragments comprising a sequence complementary to a nucleic acid of interest or a portion thereof, said process comprising the steps of:

(A) providing

(i) one or more detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into a nucleic acid; or

(ii) one or more oligonucleotides or polynucleotides comprising at least one said detectable non-radioactive chemically modified or labeled nucleotide or nucleotide analog; or

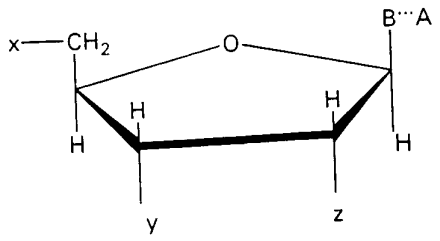
(iii) both (i) and (ii);

wherein said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs (i) and said oligonucleotides and polynucleotides (ii) are capable of attaching to or coupling to or incorporating into or forming one or more nucleic acid fragments, and wherein said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs have been modified or labeled non-disruptively or disruptively on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety or the base analog thereof; and;

(B) incorporating said one or more detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs (i) or said one or more oligonucleotides or polynucleotides comprising at least one chemically modified or labeled nucleotides or nucleotide analogs (ii), or both (i) and (ii), into one or more nucleic acid fragments, to prepare detectable non-radioactive labeled fragments, each such fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof and said one or more detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs, and wherein said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of:

X36

(i)

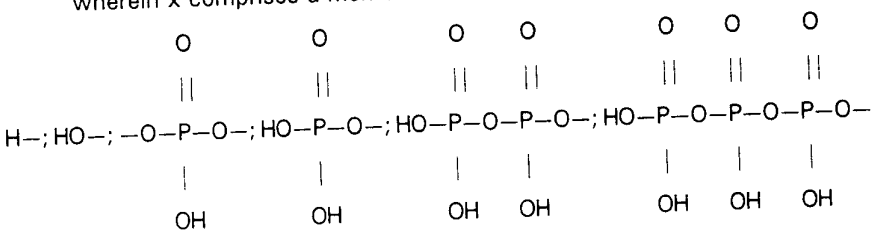


wherein B represents a purine moiety, a 7-deazapurine moiety, a pyrimidine moiety, or an analog of any of the foregoing, and B is covalently bonded to the C1-position of the sugar moiety or sugar analog, provided that whenever B is a purine, a purine analog, a 7-deazapurine moiety or a 7-deazapurine analog, the sugar moiety or sugar analog is attached at the N9 position of the purine moiety, the purine analog, the 7-deazapurine moiety or the 7-deazapurine analog thereof, and whenever B is a pyrimidine moiety or a pyrimidine analog, the sugar moiety or sugar analog is attached at the N1 position of the pyrimidine moiety or the pyrimidine analog;

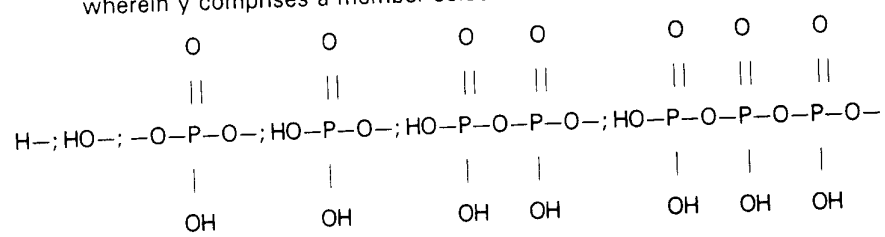
wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety capable of producing directly or indirectly a detectable non-radioactive signal; and

wherein B and A are covalently attached directly or through a linkage group, and

wherein x comprises a member selected from the group consisting of:



wherein y comprises a member selected from the group consisting of:



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wherein z comprises a member selected from the group consisting of H– and HO– ;

(ii)

Sig
|
PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety, and

wherein said PM is covalently attached to SM, said BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii)

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is detectable non-radioactive moiety; and

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

(C) transferring or subjecting said detectable non-radioactive labeled fragments to a sequencing gel;

36

(D) separating or resolving said detectable non-radioactive labeled fragments; and

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(E) non-radioactively detecting directly or indirectly the presence of said detectable non-radioactive labeled fragments to determine the sequence of said nucleic acid of interest.

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1281. (Twice Amended) The process according to claim 1177, wherein said detectable non-radioactive labeled nucleic acid fragment or fragments are terminally ligated or attached to a polypeptide.

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1291. (Amended) The process according to claim 1290, wherein said detecting step the directly detectable signal providing A or Sig detectable non-radioactive moiety comprises a member selected from the group consisting of a fluorogenic compound, a chromogenic compound, a chemiluminescent compound and an electron dense compound.

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1297. (Twice Amended) The process according to claim 1177, wherein said Sig detectable non-radioactive moiety is capable of being detected by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

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1298. (Twice Amended) A process for detecting a nucleic acid of interest in a sample, which process comprises the steps of:

(a) specifically hybridizing said nucleic acid of interest in the sample with one or more detectable non-radioactive labeled oligo- or polynucleotides, each such oligo- or polynucleotide being complementary to or capable of hybridizing with said nucleic acid of interest or a portion thereof, wherein said oligo- or polynucleotides comprise one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety or a base analog of any of the foregoing; and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof, and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization;

(ii) a nucleotide or nucleotide analog having the formula

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization; and

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(iii) a nucleotide or nucleotide analog, said nucleotide having the formula

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group, and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization;

provided that when said nucleotide or nucleotide analog (iii) is attached to an oligoribonucleotide or a polyribonucleotide, and provided that when Sig is attached through a chemical linkage to a terminal PM at the 3′ position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3′ terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide; and

(b) detecting non-radioactively the presence of said Sig detectable non-radioactive moieties in any of the detectable non-radioactive labeled oligo- or polynucleotides which have hybridized to said nucleic acid of interest.

X40

X41 1340. (Amended) The process according to claim 1298, wherein said covalent attachment in any of nucleotides (i), (ii) or (iii) does not interfere substantially with the characteristic ability of Sig to form a detectable non-radioactive signal.

X42 1349. (Amended) The process according to claim 1345, wherein said linkage group does not substantially interfere with formation of the signaling moiety or detection of the detectable non-radioactive signal.

X43 1405. (Amended) The process according to claim 1403, wherein said detecting step the directly detectable non-radioactive signal is provided by an enzyme.

X44 1409. (Twice Amended) The process according to claim 1298, wherein said Sig detectable non-radioactive moiety is capable of being detected by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

145 SUB (IIB) 1411. (Twice Amended) A process for detecting a nucleic acid of interest in a sample, which process comprises the steps of:

(A) providing:

(i) an oligo- or polynucleotide complementary to and capable of (1) specifically hybridizing to and forming a hybrid with a nucleic acid of interest or a portion thereof and (2) capable of binding to or complexing with a non-radioactively detectable protein; and

(ii) a non-radioactively detectable protein which is capable of binding to or complexing with said nucleic acid hybrid;

(B) contacting a sample suspected of containing said nucleic acid of interest with said oligo- or polynucleotide (i) and said non-radioactively detectable protein (ii) to form a complex; and

(C) detecting non-radioactively the presence of said non-radioactively detectable protein in said complex to detect said nucleic acid of interest.

SUB (IIC) 150 X46 1430. (Amended) The process according to claim 1411, wherein said oligo- or polynucleotide (i) comprises at least one protein binding nucleic acid sequence selected from the group consisting of an antibody, a promoter, a repressor and an inducer.

X47 1432. (Amended) The process according to claim 1430, wherein said at least one protein binding nucleic acid sequence is covalently attached to said oligo- or polynucleotide.

X48 1434. (Amended) The process according to claim 1432, wherein said covalent attachment does not interfere substantially with the characteristic ability of said non-radioactively detectable protein to bind to any hybrid formed between said oligo- or polynucleotide (i) and said nucleic acid of interest.

1435. (Amended) The process according to claim 1432, wherein said covalent attachment does not interfere substantially with the characteristic ability of said non-radioactively detectable protein to be detected non-radioactively when bound to any hybrid formed between said oligo- or polynucleotide (i) and said nucleic acid of interest.

X49 1448. (Amended) The process according to claim 1446, wherein said signaling component or indicator molecule comprises an aliphatic chemical moiety comprising at least four carbon atoms.

X50 1468. (Amended) The process according to claims 1467, wherein said direct detection step is carried out by a member selected from the group consisting of a fluorogenic compound, a chromogenic compound, a chemiluminescent compound, an enzyme, a radioactive compound and an electron dense compound.

X51 1471. (Twice Amended) The process according to claim 1411, wherein said nonradioactively detectable protein is capable of being detected by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

X52

1473. (Amended) A process for determining whether the number of copies of a particular chromosome in a cell is normal or abnormal, the process comprising the steps of:

contacting said cell under hybridizing conditions with one or more clones or DNA fragments, or oligo- or polynucleotides derived from said clone or clones, wherein said clones or fragments or oligo- or polynucleotides are capable of hybridizing specifically to a locus or loci of said particular chromosome or a portion thereof, wherein said clones or fragments or oligo- or polynucleotides comprise one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

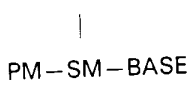
SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety or an analog of any of the foregoing thereof, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to the SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof, and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

(ii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

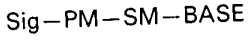
SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group,

to permit specific hybridization of said clone or clones or DNA fragments or oligo- or polynucleotides to the locus or loci of said particular chromosome;

detecting non-radioactively any specifically hybridized clone or clones or DNA fragments or oligo- or polynucleotides, and determining the number of copies of said particular chromosome; and

comparing said determined number of copies of said particular chromosome with a number of copies of said particular chromosome determined for a normal cell containing said particular chromosome, and determining whether the number of copies of said particular chromosome in said cell is abnormal.

1474. (Amended) A process for identifying a chromosome of interest in a cell containing other chromosomes, the process comprising the steps of:

providing a set of clones or DNA fragments, or oligo- or polynucleotides derived from said clone or clones, wherein said clones or fragments or oligo- or polynucleotides are specifically hybridizable to a locus or loci in said chromosome of interest, wherein said clones or fragments or said oligo- or polynucleotides comprise one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said non-radioactive modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a detectable non-radioactive moiety, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof, and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

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(ii) a nucleotide or nucleotide analog having the formula

Sig
|
PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached SM directly or through a linkage group; and

(iii) a nucleotide or nucleotide analog having the formula

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

fixing the chromosomes from or in said cell;

52 contacting said fixed chromosomes under hybridizing conditions with said set of clones or DNA fragments or oligo- or polynucleotides, permitting specific hybridization of said set of clones or DNA fragments or oligo- or polynucleotides to said locus or loci in said chromosome of interest;

detecting non-radioactively any of said clones or DNA fragments or oligo- or polynucleotides which have specifically hybridized to said locus or loci in said chromosome of interest, and obtaining a pattern of hybridizations between said set of clones or DNA fragments or oligo- or polynucleotides and said chromosomes; and

identifying said chromosome of interest by means of said hybridization pattern obtained.

1475. (Amended) A process for identifying a plurality or all of the chromosomes in a cell of interest, the process comprising the steps of:

providing sets of clones or DNA fragments, or oligo- or polynucleotides derived from said clones, wherein said clones or fragments or said oligo- or polynucleotides are capable of hybridizing specifically to a locus or loci in a chromosome of said cell of interest, wherein each of said clones or DNA fragments or oligo- or polynucleotides in said sets are labeled with a different indicator molecule and each of said clones or DNA fragments or oligo- or polynucleotides comprises one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said detectable non-radioactive modified or labeled nucleotide or nucleotide analog are selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

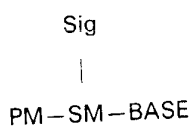
BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a detectable non-radioactive moiety,

X52

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine or a pyrimidine analog, at a position other than the C8 position when BASE is a purine or a purine analog, and at a position other than the C7 position when BASE is a 7-deazapurine or a 7-deazapurine analog thereof;

(ii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii) a nucleotide or nucleotide analog having the formula

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

X52

fixing the chromosomes from or in said cell;

contacting said fixed chromosomes under hybridizing conditions with said sets of clones or DNA fragments or oligo- or polynucleotides, and permitting specific hybridization of said sets of clones or DNA fragments or oligo- or polynucleotides to the locus or loci in said chromosomes; and

detecting non-radioactively any of said different indicator molecules in said sets of clones or DNA fragments or oligo- or polynucleotides which have specifically hybridized to the locus or loci in said chromosomes, and identifying any one of the chromosomes in said cell of interest.

1476. (Amended) A process for determining the number of chromosomes in an interphase cell of interest, the process comprising the steps of:

providing sets of clones or DNA fragments or oligo- or polynucleotides derived from said clones, wherein said set of clones or DNA fragments or oligo- or polynucleotides are specifically complementary to or specifically hybridizable with at least one locus or loci in a chromosome of said interphase cell of interest and each of said clones or DNA fragments or oligo- or polynucleotides in said sets comprises one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

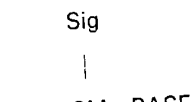
SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine moiety or a pyrimidine analog, at a position other than the C8 position when BASE is a purine or a purine analog, and at a position other than the C7 position when BASE is a 7-deazapurine or a 7-deazapurine analog;

(ii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

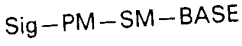
SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached SM directly or through a linkage group; and

(iii) a nucleotide or nucleotide analog, said nucleotide having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is detectable non-radioactive moiety,

wherein PM is covalently attached to the SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

contacting said interphase cell under hybridizing conditions with said sets of clones or DNA fragments or oligo- or polynucleotides, and permitting specific hybridization of said sets of clones or DNA fragments or oligo- or polynucleotides to any of the locus or loci in said chromosomes;

detecting non-radioactively any of said sets of clones or DNA fragments or oligo- or polynucleotides specifically hybridized to the locus or loci in said chromosomes, to obtain a pattern of generated signals; and comparing each generated signal with other generated signals in said pattern, and determining the number of chromosomes in said interphase cell of interest.

X52

X53 1499. (Amended) The process according to any of claims 1473, 1474, 1475 or 1476, wherein said covalent attachment in any of nucleotides (i), (ii) or (iii) does not interfere substantially with the characteristic ability of Sig to form a detectable non-radioactive signal.

X54 1507. (Amended) The process according to claim 1504, wherein said linkage group does not substantially interfere with formation of the signaling moiety or detection of the detectable non-radioactive signal.

X55 1565. (Amended) The process according to claim 1564, wherein said detecting step is carried out by means of a member selected from the group consisting of a fluorogenic compound, a chromogenic compound, a cherniluminescent compound and an electron dense compound.

1566. (Amended) The process according to claim 1564, wherein said detecting step the directly detectable non-radioactive signal is provided by an enzyme.

X56

1570. (Twice Amended) The process according to any of claims 1473, 1474, 1475 or 1476, wherein said Sig detectable non-radioactive moiety is capable of being detected by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

X57

1582. (Twice Amended) A process for preparing a detectable non-radioactively labeled oligo- or polynucleotide of interest, comprising the steps of:

(A) providing either:

(1) one or more detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA or an oligo- or polynucleotide of interest, alone or in conjunction with one or more other modified or unmodified nucleic acids selected from the group consisting of nucleotides, oligonucleotides and polynucleotides, wherein said other modified or unmodified nucleic acids are capable of incorporating into an oligo- or polynucleotide of interest, and wherein said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs comprise one or more signaling moieties which are capable of providing directly or indirectly a detectable non-radioactive signal; or

(2) an oligo- or polynucleotide of interest comprising one or more said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs, alone or in conjunction with one or more other modified or unmodified nucleic acids selected from the group consisting of nucleotides, oligonucleotides and polynucleotides;

wherein said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate moiety, the base moiety or the base analog, and are selected from the group consisting of:

(i)

PM–SM–BASE–Sig

wherein

PM is a phosphate moiety or phosphate analog,

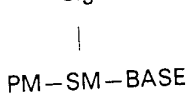
SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a detectable non-radioactive moiety, and

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof, and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

(ii)



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a detectable non-radioactive moiety, and

wherein said PM is covalently attached to SM, said BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii)

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is detectable non-radioactive moiety; and

wherein PM is covalently attached to SM, BASE is covalently attached SM, and Sig is covalently attached to PM directly or through a linkage group;

provided that when said nucleotide or nucleotide analog (iii) is attached to an oligoribonucleotide or a polyribonucleotide, and provided that when Sig is attached through a chemical linkage to a terminal PM at the 3′ position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3′ terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide; and

said oligo- or polynucleotide of interest; and

(B) either incorporating said one or more detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs (A)(1) into said oligo- or polynucleotide, and preparing a non-radioactive labeled oligo- or polynucleotide of interest, or preparing said oligo- or polynucleotide of interest from said oligo- or polynucleotide recited in step (A)(2) above.

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X58

1608. (Amended) The process according to claim 1582, wherein said one or more detectable non-radioactive chemically modified nucleotides or said other modified or unmodified nucleic acids comprise a nucleoside di- or tri-phosphate.

X59 1624. (Amended) The process according to claim 1623, wherein said linkage group does not substantially interfere with formation of the signaling moiety or detection of the detectable non-radioactive signal.

X60 1628. (Amended) The process according to claim 1627, wherein said linkage group does not substantially interfere with formation of the signaling moiety or detection of the detectable non-radioactive signal.

X61 1632. (Amended) The process according to claim 1631, wherein said linkage group does not substantially interfere with formation of the signaling moiety or detection of the detectable non-radioactive signal.

X62 1639. (Amended) The process according to claim 1582, wherein said covalent attachment in any of nucleotides (i), (ii) or (iii) does not interfere substantially with the characteristic ability of Sig to form a detectable non-radioactive signal.

X63 1647. (Amended) The process according to claim 1645, wherein said linkage group does not substantially interfere with formation of the signaling moiety or detection of the detectable non-radioactive signal.

X64 1686. (Amended) The process according to claim 1582, wherein said Sig is detectable non-radioactively when the oligo- or polynucleotide is contained in a double-stranded ribonucleic or deoxyribonucleic acid duplex.

1687. (Amended) The process according to claim 1582, wherein said Sig is detectable non-radioactively when it is attached to the nucleotide directly or through a linkage group.

X64 1688. (Amended) The process according to claim 1687, wherein said linkage group does not interfere substantially with the characteristic ability of Sig to form a detectable non-radioactive signal.

X65 1696. (Amended) The process according to claim 1695, wherein said directly detectable signal providing Sig detectable non-radioactive moiety is selected from the group consisting of a fluorogenic compound, a chromogenic compound, a chemiluminescent compound, an electron dense compound and an enzyme.

X66 1699. (Twice Amended) The process according to claim 1582, wherein said Sig detectable non-radioactive moiety is capable of being detected by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

SUB 21 X67 1700. (Amended) A process for determining the sequence of a nucleic acid of interest, comprising the steps of:

providing or generating non-radioactive labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs comprise one or more chelating compounds or chelating components capable of chelating a radioactive metal and providing a detectable radioactive signal, and wherein said one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety, or the base analog thereof;

subjecting said labeled fragments to a sequencing gel to separate or resolve said fragments; and

X67

detecting the presence of each of said separated or resolved fragments by means of the detectable radioactive signal provided by a radioactive metal chelated by said chelating compounds or chelating components in the detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, and determining the sequence of said nucleic acid of interest.

X68

SUB 2

1701. (Twice Amended) A process for determining the sequence of a nucleic acid of interest, comprising the steps of:

providing or generating detectable non-radioactive labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs comprise one or more chelating compounds or chelating components capable of chelating a radioactive metal and providing a detectable radioactive signal, and wherein said one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety, or the base analog thereof;

introducing or subjecting said fragments to a sequencing gel;

separating or resolving said fragments in said sequencing gel; and

detecting each of the separated or resolved fragments by means of the detectable radioactive signal provided by a radioactive metal chelated by said chelating compounds or chelating components in the detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, and determining the sequence of said nucleic acid of interest.

1702. (Twice Amended) A process for determining the sequence of a nucleic acid of interest, comprising the steps of:

providing or generating detectable non-radioactive labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs comprise one or more chelating compounds or chelating components capable of chelating a radioactive metal and providing a detectable radioactive signal, and wherein said one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety or the base analog thereof;

radioactively detecting with a sequencing gel the detectable non-radioactive labeled nucleic acid fragments by means of a radioactive metal chelated by said chelating compounds or chelating components; and

determining the sequence of said nucleic acid of interest.

1703. (Twice Amended) A process for determining the sequence of a nucleic acid of interest, comprising the step of detecting with a sequencing gel one or more detectable non-radioactive labeled nucleic acid fragments comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs comprise one or more chelating compounds or chelating components capable of chelating a radioactive metal and providing a detectable radioactive signal, and wherein said one or more detectable non-radioactive modified nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the base moiety or the base analog thereof.

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1704. (Twice Amended) A process for determining in a sequencing gel the presence of nucleic acid fragments comprising a sequence complementary to a nucleic acid sequence of interest or a portion thereof, said process comprising the steps of:

(A) providing

(i) one or more detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into a nucleic acid, or

(ii) one or more oligonucleotides or polynucleotides comprising at least one of said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs; or

(iii) both (i) and (ii);

wherein said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs (i) and said oligonucleotides and polynucleotides (ii) are capable of attaching to or coupling to or incorporating into or forming one or more nucleic acid fragments, wherein said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs comprise one or more chelating compounds or chelating components capable of chelating a radioactive metal and providing a detectable radioactive signal, and wherein said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs have been modified non-disruptively or disruptively on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety or the base analog thereof; and;

(B) incorporating said one or more detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs (i) or said one or more oligonucleotides or polynucleotides comprising at least one of said detectable non-radioactive chemically modified or labeled nucleotides (ii), or both (i) and (ii), into said one or more nucleic acid fragments, to prepare detectable non-radioactive labeled fragments, each such fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, said detectable non-radioactive labeled fragments further comprising one or more detectable non-radioactive

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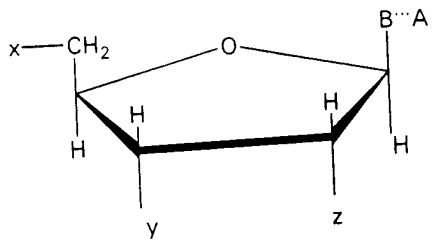
chemically modified nucleotides or nucleotide analogs selected from the group consisting of:

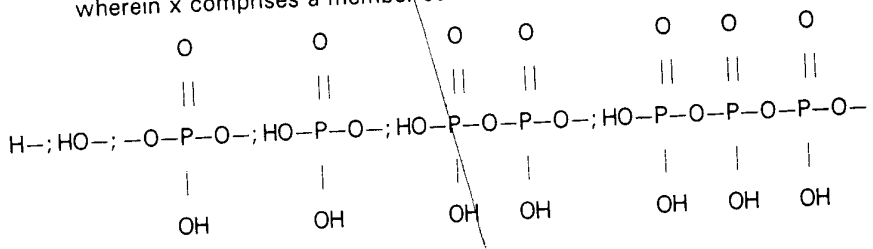


wherein B represents a purine moiety, a 7-deazapurine moiety, a pyrimidine moiety, or an analog of any of the foregoing, and B is covalently bonded to the C1'-position of the sugar moiety or sugar analog, provided that whenever B is a purine, a purine analog, a 7-deazapurine moiety or a 7-deazapurine analog, the sugar moiety or sugar analog is attached at the N9 position of the purine moiety, the purine analog, the, 7-deazapurine moiety or the 7-analog thereof, and whenever B is a pyrimidine moiety or a pyrimidine analog, the sugar moiety or sugar analog is attached at the N1 position of the pyrimidine moiety or the pyrimidine analog;

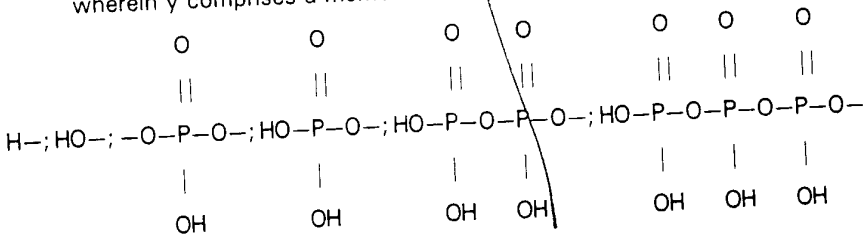
wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing directly or indirectly a detectable radioactive signal; and

wherein B and A are covalently attached directly or through a linkage group, and

wherein x comprises a member selected from the group consisting of:



wherein y comprises a member selected from the group consisting of:



X66

wherein z comprises a member selected from the group consisting of H- and HO-

(ii)

wherein

PM is a phosphate moiety or phosphate analog,

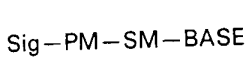
SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, and

wherein said PM is covalently attached to SM, said BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii)



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog,

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal; and

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

(C) transferring or subjecting said labeled fragments to a sequencing gel;

(D) separating or resolving said labeled fragments; and

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(E) detecting directly or indirectly the presence of said labeled fragments by means of a radioactive metal chelated by said chelating compounds or chelating components.

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1705. (Amended) A process for detecting a nucleic acid of interest in a sample, which process comprises the steps of:

SUB 23

(a) specifically hybridizing said nucleic acid of interest in the sample with one or more oligo- or polynucleotides, each such oligo- or polynucleotide being complementary to or capable of hybridizing with said nucleic acid of interest or a portion thereof, wherein said oligo- or polynucleotides comprise one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

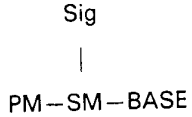
SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety or a base analog of any of the foregoing; and

Sig is a signaling moiety comprising a chelating compound or component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof and at a position other than the C7 position when BASE is a 7-

deazapurine moiety or an analog thereof, and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization;

(ii) a nucleotide or nucleotide analog having the formula



wherein

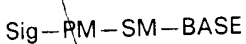
PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or component capable of providing chelating a radioactive metal and a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization; and

(iii) a nucleotide or nucleotide analog, said nucleotide having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or components capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group, and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization;

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provided that when said nucleotide or nucleotide analog (iii) is attached to an oligoribonucleotide or a polyribonucleotide, and provided that when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide; and

(b) detecting radioactively the presence of said signaling moieties Sig in any of the oligo-or polynucleotides which have hybridized to said nucleic acid of interest by means of a radioactive metal chelated by said chelating compounds or chelating components.

1706. (Amended) A process for detecting a nucleic acid of interest in a sample, which process comprises the steps of:

(A) providing:

(i) an oligo- or polynucleotide having two segments:

(a) a first segment complementary to and capable of hybridizing to a portion of said nucleic acid of interest; and

(b) a second segment comprising at least one protein binding sequence; and

(ii) a detectable protein capable of binding to said protein binding sequence and comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal;

(B) contacting a sample suspected of containing said nucleic acid of interest with said oligo- or polynucleotide (i) and said detectable protein (ii) to form a complex;

(C) detecting radioactively the presence of said protein in said complex and said nucleic acid of interest by means of a radioactive metal chelated by said chelating compound or chelating component.

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SUB 24

1707. (Twice Amended) A process for determining whether the number of copies of a particular chromosome in a cell is normal or abnormal, the process comprising the steps of:

contacting said cell under hybridizing conditions with one or more clones or DNA fragments, or oligo- or polynucleotides derived from said clone or clones, wherein said clones or fragments or oligo- or polynucleotides are capable of hybridizing specifically to a locus or loci of said particular chromosome or a portion thereof, wherein said clones or fragments or oligo- or polynucleotides comprise one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs , which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

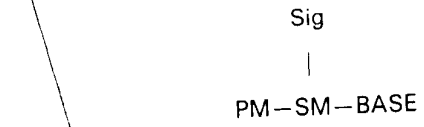
PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety or an analog of any of the foregoing thereof, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to the SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof, and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

(ii) a nucleotide or nucleotide analog having the formula



wherein

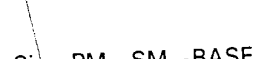
PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group, to permit specific hybridization of said clone or clones or DNA fragments or oligo- or polynucleotides to the locus or loci of said particular chromosome;

detecting radioactively the signal generated by said specifically hybridized clone or clones or DNA fragments or oligo- or polynucleotides by means of a radioactive metal chelated by said chelating compound or chelating component, and determining the number of copies of said particular chromosome; and

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comparing said determined number of copies of said particular chromosome with a number of copies of said particular chromosome determined for a normal cell containing said particular chromosome, and determining whether the number of copies of said particular chromosome in said cell is abnormal.

1708. (Amended) A process for identifying a chromosome of interest in a cell containing other chromosomes, the process comprising the steps of:

providing a set of clones or DNA fragments, or oligo- or polynucleotides derived from said clone or clones, wherein said clones or fragments or oligo- or polynucleotides are specifically hybridizable to a locus or loci in said chromosome of interest, wherein said clones or fragments or oligo- or polynucleotides comprise one or more detectable modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

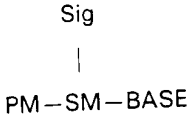
SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof, and

at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

(ii) a nucleotide or nucleotide analog having the formula



wherein

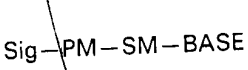
PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached SM directly or through a linkage group; and

(iii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

fixing the chromosomes from or in said cell;

contacting said fixed chromosomes under hybridizing conditions with said set of clones or DNA fragments or oligo- or polynucleotides, permitting specific hybridization of said set of clones or DNA fragments or oligo- or polynucleotides to said locus or loci in said chromosome of interest;

detecting radioactively by means of a radioactive metal chelated by said chelating compound or chelating component any signal generated by each of said clones or DNA fragments or oligo- or polynucleotides which have specifically hybridized to said locus or loci in said chromosome of interest, and obtaining a pattern of hybridizations between said set of clones or DNA fragments or oligo- or polynucleotides and said chromosomes; and

identifying said chromosome of interest by means of said hybridization pattern obtained.

1709. (Amended) A process for identifying a plurality or all of the chromosomes in a cell of interest, the process comprising the steps of:

providing sets of clones or DNA fragments, or oligo- or polynucleotides derived from said clones, wherein each of said set of clones or DNA fragments or oligo- or polynucleotides are specifically hybridizable to a locus or loci in a chromosome of said cell of interest, wherein each of said clones or DNA fragments or oligo- or polynucleotides in said sets are labeled with a different indicator molecule and each of said clones or DNA fragments or oligo- or polynucleotides comprise one or more detectable modified or labeled nucleotides or nucleotide analogs capable of detection, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said modified or labeled nucleotide or nucleotide analogs are selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

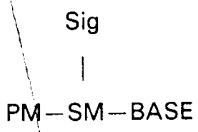
PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine. or a pyrimidine analog, at a position other than the C8 position when BASE is a purine or a purine analog, and at a position other than the C7 position when BASE is a 7-deazapurine or a 7-deazapurine analog thereof;

(ii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

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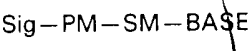
(iii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

fixing the chromosomes from or in said cell;

contacting said fixed chromosomes under hybridizing conditions with said sets of clones or DNA fragments or oligo- or polynucleotides, and permitting specific hybridization of said sets of clones or DNA fragments or oligo- or polynucleotides to the locus or loci in said chromosomes; and

detecting radioactively by means of a radioactive metal chelated by said chelating compound or chelating component any signal generated by each of said different indicator molecules in said sets of clones or DNA fragments or oligo- or polynucleotides which have specifically hybridized to the locus or loci in said chromosomes, and identifying any one of the chromosomes in said cell of interest.

1710. (Amended) A process for determining the number of chromosomes in an interphase cell of interest, the process comprising the steps of:

providing sets of clones or DNA fragments, or oligo- or polynucleotides derived from said clones, wherein each of said set of clones or DNA fragments or oligo- or polynucleotides are specifically complementary to or specifically hybridizable with at least one locus or loci in a chromosome of said interphase cell of interest, wherein each of said clones or DNA fragments or oligo- or polynucleotides in said sets comprise one or more detectable modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said modified or labeled nucleotide or nucleotide analog are selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine moiety or a pyrimidine analog, at a position other than the C8 position when BASE is a purine or a purine analog, and at a position other than the C7 position when BASE is a 7-deazapurine or a 7-deazapurine analog;

(ii) a nucleotide or nucleotide analog having the formula

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached SM directly or through a linkage group; and

(iii) a nucleotide or nucleotide analog, said nucleotide having the formula

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to the SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

contacting said interphase cell under hybridizing conditions with said sets of clones or DNA fragments or oligo- or polynucleotides, and permitting specific hybridization of said sets of clones or DNA fragments or oligo- or polynucleotides to any of the locus or loci in said chromosomes;

detecting radioactively by means of a radioactive metal chelated by said chelating compound or chelating component any signals generated by each of said sets of clones or DNA fragments or oligo- or polynucleotides specifically hybridized to the locus or loci in said chromosomes, to obtain a pattern of generated signals; and comparing each generated signal with other generate signals in said pattern, and determining the number of chromosomes in said interphase cell of interest.

1711. (Amended) A process for preparing a labeled oligo- or polynucleotide of interest, comprising the steps of:

(A) providing either:

(1) one or more detectable chemically modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached

to or coupled to or incorporated into DNA or RNA or an oligo- or polynucleotide of interest, alone or in conjunction with one or more other modified or unmodified nucleic acids selected from the group consisting of nucleotides, oligonucleotides and polynucleotides, wherein said other modified or unmodified nucleic acids are capable of incorporating into an oligo- or polynucleotide of interest, and wherein said chemically modified or labeled nucleotides or nucleotide analogs comprise one or more signaling moieties comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, or

(2) an oligo- or polynucleotide of interest comprising one or more of said detectable chemically modified or labeled nucleotides or nucleotide analogs, alone or in conjunction with one or more other modified or unmodified nucleic acids selected from the group consisting of nucleotides, oligonucleotides and polynucleotides,

wherein said chemically modified or labeled nucleotides or nucleotide analogs are modified on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate moiety, the base moiety or the base analog, and are selected from the group consisting of:

(i)

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

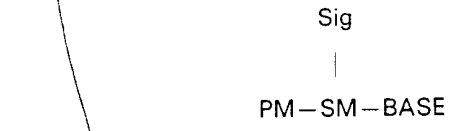
BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, and

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or

an analog thereof, and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

(ii)



wherein

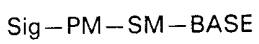
PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a radioactive signal, and wherein said PM is covalently attached to SM, said BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii)



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal; and wherein PM is covalently attached to SM, BASE is covalently attached SM, and Sig is covalently attached to PM directly or through a linkage group, provided that when said nucleotide or nucleotide analog (iii) is attached to an oligoribonucleotide or a polyribonucleotide, and provided that when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide; and said oligo- or polynucleotide of interest;

and

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(B) either incorporating said one or more modified or labeled nucleotides or nucleotide analogs (A)(1) into said oligo- or polynucleotide, and preparing a labeled oligo- or polynucleotide of interest, or preparing said oligo- or polynucleotide of interest from said oligo- or polynucleotide recited in step (A)(2) above.

X72 1712. (Amended) A process for detecting the presence of a nucleic acid of interest in a sample, comprising the steps of:

providing or generating (i) one or more detectable non-radioactively labeled oligonucleotides or polynucleotides, each of said detectable non-radioactively labeled oligonucleotides or polynucleotides comprising a sequence sufficiently complementary to said nucleic acid of interest or to a portion thereof to specifically hybridize therewith, wherein said one or more detectable non-radioactively labeled oligonucleotides or polynucleotides comprise one or more detectable non-radioactively modified or labeled nucleotides or nucleotide analogues, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said detectable non-radioactively modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety, or the base analog thereof, and (ii) a sample that may contain said nucleic acid of interest;

forming in liquid phase hybrids comprising said one or more detectable non-radioactively labeled oligonucleotides or polynucleotides specifically hybridized with said nucleic acid of interest;

separating or resolving in a gel said formed hybrids; and

detecting non-radioactively the separated or resolved hybrids to detect the presence of said nucleic acid of interest.

X73 1725 (Amended) The process according to claim 1400, wherein said direct detection is carried out with the same indicator molecules.

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1726. (Amended) The process according to claim 1400, wherein said direct detection is carried out with different indicator molecules.

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